CHAPTER 153

Infant Botulism

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Of the three forms of human botulism (food-borne, wound, and infant), infant botulism is the most recently recognized (1976) and the most common in the United States. Now recognized globally, infant botulism results from a unique pathogenesis. Ingested spores of *Clostridium botulinum* germinate, colonize the infant colon, and produce botulinum neurotoxin. The toxin then is absorbed, binds to peripheral cholinergic synapses, and causes flaccid paralysis. Knowledge of this intestinal pathogenesis resulted in the discovery of novel pathogenic strains of *Clostridium baratii* and *Clostridium butyricum,* each of which can make a botulinum-like neurotoxin and cause the clinical picture of infant botulism. Discovery of these strains enlarged the number of organisms known to cause the "intestinal toxemias of infancy," of which infant botulism is the prototype.[4] Parenthetically, adults and older children rarely may become susceptible to infant-type botulism after broad-spectrum antibiotic treatment, intestinal surgery, or inflammatory bowel disease[6, 22, 29, 49] or in association with Meckel diverticulum or bone marrow transplantation procedures.[74]

History

Infant botulism is not a new disease; rather, it is a recently recognized one. The first laboratory-proven case of human infant botulism occurred in California in 1931, although it was misdiagnosed at the time.[13] Decades later and well before the etiology of the disease was apparent, the characteristic clinical features of infant botulism had become evident to discerning observers. In 1974, Grover and associates[34] described nine patients from Pennsylvania with a neurologic syndrome of undetermined cause that from today's perspective almost certainly was infant botulism. The same idiopathic syndrome was recognized in southern California and was reported by Ramseyer and colleagues[67] in 1976 to have a characteristic electromyographic pattern. In 1977, Clay and associates[23] linked their eight patients to infant botulism.

The first report of frank botulism in infancy was described by Pickett and colleagues[66] in 1976. Although the

source of botulinum neurotoxin in their two patients was undetermined, the possibility of in vivo production of it was suggested.[51, 66] The diagnosis of botulism in these and other California patients was established by identification of *C. botulinum* toxin and organisms in the infants' feces.[51] Evidence also was obtained that ingested spores of *C. botulinum* had produced the toxin in the infants' intestinal tract.[9, 51, 94]

In subsequent years, the clinical spectrum of infant botulism was found to include mild, outpatient cases and, in some but not all[18] locations, sudden unexpected death indistinguishable from typical sudden infant death syndrome.[10, 58, 65, 79, 90] In 1985, a *C. baratii* strain that produced a type F–like botulinum neurotoxin was recognized belatedly as the true cause of a case of infant botulism that occurred in New Mexico in 1979,[35, 38] and in 1986, a *C. butyricum* strain that produced a type E–like botulinum neurotoxin was recognized as the cause of two cases of infant botulism in Rome, Italy.[14] These latter two novel clostridia were discovered only because they caused human infant botulism; their existence suggests that others like them await discovery.

Etiologic Agent

C. botulinum is a gram-positive, spore-forming, obligate anaerobe for which the natural habitat worldwide is the soil. Consequently, *C. botulinum* is as ubiquitous as the dust on which it may travel, and, hence, its spores commonly are present on fresh fruits, vegetables, and other agricultural products such as honey. Strains of *C. botulinum* are so diverse in their biochemical capabilities that they would not be grouped as a single species except for the similar neurotoxin molecule that each strain produces[78]; at present, *C. botulinum* is subdivided into six groups based on metabolic characteristics.[62] Almost all cases of infant botulism in the United States have been caused by group I proteolytic type A or type B strains. Unusual strains of *C. baratii* and *C. butyricum* that make botulinum-like toxins E and F also cause infant botulism.[14, 35, 62, 83, 93]

In general, each vegetative cell of *C. botulinum* produces just one of seven serologically distinguishable toxins, which arbitrarily have been assigned the letters A to G. Antitoxin raised against one toxin type does not protect against any of the other six types. The different toxin types serve as convenient epidemiologic and clinical markers. Each toxin molecule is a simple protein consisting of two polypeptide chains of approximately 100,000 d (heavy chain) and 50,000 d (light chain) joined by a disulfide bond. Botulinum toxin is the most poisonous substance known.[31] For this reason and because of the ease with which it may be produced, transported, and disseminated, the Centers for Disease Control and Prevention (CDC) has listed botulinum toxin as one of the six "class A" (most dangerous) potential bioweapon agents.[12] By extrapolation from studies involving adult primates, the lethal dose in the bloodstream of humans is approximately 1 ng/kg body weight.[12, 31] Its potency in infants may be even higher because of the narrowness of their pharyngeal airway.[91]

After centuries of evoking awe and mystery, the basis of the phenomenal potency of the botulinum (and tetanus) toxins was shown to be enzymatic. The light chain of each neurotoxin is a Zn^{2+}-containing protease that hydrolyzes one or more of three intracellular proteins needed for vesicle fusion and acetylcholine release into the synaptic cleft.[55, 60]

Pathogenesis

Infant botulism is not the diminutive form of food-borne botulism and, hence, is not "infantile botulism." Rather, infant botulism results from a unique infectious disease pathway and was so named to emphasize that fact.[2, 4, 51] Ingested spores of *C. botulinum* germinate, colonize the infant colon, and produce botulinum neurotoxin.[9, 36, 53, 54, 63, 94] The toxin subsequently is absorbed and carried by the bloodstream to peripheral cholinergic synapses, to which it binds irreversibly. The light chain then is taken into the cytosol of the neuron, where it blocks the release of acetylcholine by enzymatic cleavage of "fusion complex" proteins.[55,60] Clinically, the most important of the peripheral cholinergic synapses is the neuromuscular junction; the toxin's action results in flaccid paralysis and hypotonia. Preganglionic cholinergic synapses in the autonomic nervous system also may be affected.[48,72]

By use of a mouse model system of intestinal colonization (in which the animals paradoxically remained symptom-free), Sugiyama and colleagues[17, 54, 84] demonstrated that the intestinal microflora of adult animals ordinarily prevents colonization of the gut by *C. botulinum*. Administration of 10^6 type A spores failed to colonize the intestine of normal adult mice, whereas after treatment for 2½ days with a combination of oral erythromycin and kanamycin, half the mice could be colonized by just 2×10^4 spores. When the antibiotic-treated mice were placed in cages with normal mice, they lost their susceptibility to intestinal colonization after 3 days.[17] (Mice normally are coprophagic.) In addition, adult germ-free mice could be colonized intestinally by just 10 *C. botulinum* type A spores. When the germ-free adult animals were placed in a room with conventional mice, in 3 days the formerly germ-free animals became resistant to colonization by 10^5 spores.[54]

In contrast to the experimental work with adult mice, normal infant mice were susceptible to intestinal colonization by *C. botulinum* spores.[84] Like human infants, the normal infant mice were susceptible to colonization for only a limited period (7 to 13 days of age). Susceptibility of the infant mice peaked between days 8 and 11 in a pattern reminiscent of the peaking of susceptibility seen between 2 and 4 months of age in human infant botulism[7, 84] (Fig. 153–1). The infective dose of spores for infant mice was much smaller than that of their antibiotic-treated adult counterparts; the 50 percent infective dose for normal infants was only 700 spores. In one experiment, just 10 spores colonized an infant mouse.[84] The minimal infective dose of *C. botulinum* spores for human infants is not known, but from exposure to spore-containing honey, it has been estimated to be as low as 10 to 100.[11]

Recognition of the central role of the host intestinal microflora in determining susceptibility or resistance to colonization by *C. botulinum* has directed attention to factors that may influence the composition of the normal microflora. Diet may be the most important of these factors. When compared with adult-type flora, infant flora is simpler, with fewer genera and species. The dominant members vary, depending in part on whether the infant is fed only breast milk, only formula milk, or a mixture of the two.[81] In addition, the composition of the intestinal flora is changed if solid foods such as cereal become part of the infant's diet. The normal human infant microflora contains several bacterial species, mainly *Bifidobacterium* and *Bacteroides,* that in vitro can inhibit the multiplication of *C. botulinum.*[86]

The onset of infant botulism occurs at a significantly younger age in formula-fed infants (7.6 weeks) than in breast-fed infants (13.7 weeks),[8] perhaps reflecting the earlier availability in formula-fed infants of suitable ecologic niches[8, 48, 81, 82] and the formula-fed infants' lack of immune factors (e.g., secretory IgA, lactoferrin) contained in human milk.[2, 3, 33] In addition, the introduction of solid foods may

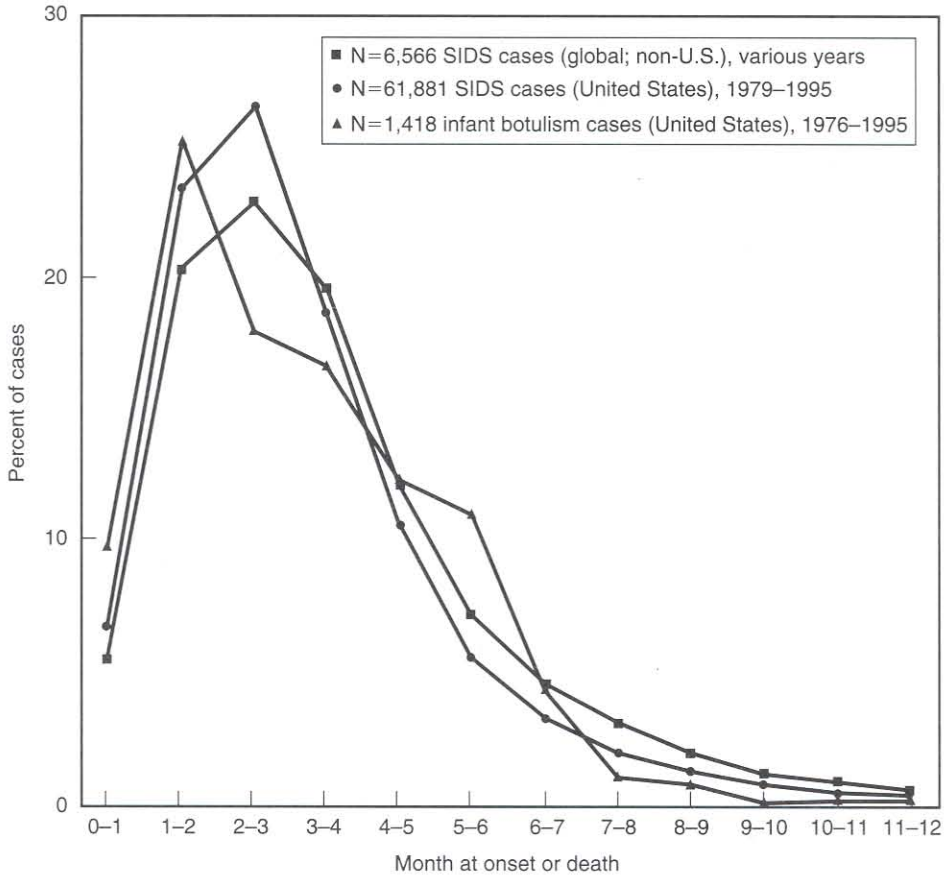

FIGURE 153–1 ■ Age distributions of infant botulism and sudden infant death syndrome (SIDS).

"perturb" the intestinal microflora[81] and thereby aid *C. botulinum* colonization.[2, 7, 48, 80]

An additional physiologic risk factor for infant botulism is slower gut motility, as measured by the frequency of defecation before the onset of illness.[80] Less than one bowel movement per day is a risk factor for both breast-fed and formula-fed infants, but it occurred in just 50 percent of cases.[73] Whether a Meckel diverticulum may predispose to the acquisition of infant botulism caused by *C. botulinum,* as it appears to do for infant botulism caused by *C. butyricum,* is not known.[28, 70]

Epidemiology

Any discussion of the epidemiology of infant botulism should be prefaced by the caveat that almost all information presently available is derived from study of only part of the clinical spectrum, namely, hospitalized patients. Accordingly, current perspectives may need to be modified as the outpatient and sudden-death portions of the clinical spectrum become defined more fully. Furthermore, the perceived incidence remains more a reflection of physician awareness and access to diagnostic testing than of the actual occurrence of disease. Almost half (41.6%) of U.S. cases have been reported from California, which has the largest number of births of any state. However, California does not have the highest incidence of infant botulism once adjustment is made for differences in annual births (Table 153–1). Notably, 8 of the 11 states with the highest incidence are located west of the Rocky Mountains, and 6 of the 8 are contiguous.

A unique epidemiologic feature of infant botulism is its age distribution, which perhaps coincidentally, is virtually identical to the age distribution of sudden infant death syndrome[7, 10, 19, 80] (see Fig. 153–1). All cases of infant botulism reported to date have occurred in children younger than 1 year. Some 95 percent of cases occur in the first 6 months of life; the remaining 5 percent are distributed over the subsequent 6 months. The youngest known patient was 6 days old at onset,[41,89] and the oldest was 351 days.[39] The illness has occurred in all major racial and ethnic groups and in approximately equal proportions in males and females. A national seasonality is not evident.

Infant botulism has been reported from all inhabited continents except Africa. In the United States, with four exceptions, all hospitalized cases known as of December

TABLE 153–1 ■ CASES AND INCIDENCE OF INFANT BOTULISM, TOP 11 STATES IN INCIDENCE, UNITED STATES, 1977–2001

State	Cases	Incidence*
Delaware	32	12.4
Hawaii	43	9.0
Utah	78	7.6
California	799	6.2
Pennsylvania	224	5.5
Oregon	40	3.7
Washington	63	3.4
Idaho	15	3.2
New Jersey	86	3.0
New Mexico	21	3.0
Nevada	21	2.9

*Per 100,000 live births per year. Montana was the state with the 12th highest incidence at 2.5.

2001 were caused by either *C. botulinum* type A or type B (or in one case, by both). Forty-nine of the 50 states, representing all regions of the country, including Alaska and Hawaii, now have reported infant botulism. Only Rhode Island has not. In general, the distribution of cases by toxin type has paralleled the distribution of toxin types in U.S. soils,[77] with type B cases predominating from the great plains eastward and type A cases predominating from the Rocky Mountains westward. Of the four exceptional toxin types, two cases in New Mexico and Oregon resulted from a type F–like toxin produced by *C. baratii* strains,[35, 38, 62] and the other two cases were caused by a *C. botulinum* strain that produced mostly type B and some type F toxin (designated type Bf). One patient with Bf illness lived in New Mexico, and the other patient had traveled there immediately before the onset of illness. A third type Bf case occurred in England.[76]

Geographic clustering has been noted. In Pennsylvania, 43 of 53 cases in the period 1977 to 1983 occurred in four suburban counties that form an arc bordering the city of Philadelphia.[47] In Colorado, three type A cases occurred in separate families in a small town with approximately 300 annual births. Two of the infants had used the same crib sequentially; environmental samples, including the crib, soil, and household dust, yielded *C. botulinum* type A.[42] In California, two type A cases occurred 5 years apart in the children of two families who lived one house apart. In another California family, two infants born successively each acquired type A infant botulism, but the third child born in sequence did not. Soil and dust specimens from the house where all three infants lived contained *C. botulinum* type A.

The role of breast-feeding and formula-feeding as factors possibly predisposing to the development of illness remains unsettled. All studies to date have identified an association between being breast-fed and being hospitalized for infant botulism.[3, 8, 47, 48, 56, 80, 90] This finding has resulted in one perspective that holds that breast-feeding predisposes to the development of illness,[47, 48, 80] whereas the other perspective holds that breast-feeding slows its onset sufficiently to permit hospitalization to occur.[2, 3, 7, 8] However, among hospitalized patients, the mean age at onset of botulism in formula-fed infants (7.6 weeks) was significantly younger and approximately half that of breast-fed infants (13.8 weeks). In addition, the fulminant-onset infant botulism patients who stopped breathing and died at home all were formula-fed.[8] The relative susceptibility of formula-fed and breast-fed infants to the acquisition of infant botulism and the resultant severity of their disease may reflect differences in the availability of suitable ecologic niches in the intestinal flora for *C. botulinum*, differences in the availability of immune factors (such as lactoferrin and secretory IgA) contained in human milk but not in formula milk,[33] or other differences not identified yet.

Honey is the one dietary reservoir of *C. botulinum* spores thus far definitively linked to infant botulism by both laboratory and epidemiologic evidence.* To date, 35 instances worldwide are known in which *C. botulinum* spores have been found in the actual honey fed to an affected infant before the onset of illness. In each instance, the toxin type (A or B) of the spores in the honey matched the toxin type (A or B) of the *C. botulinum* that caused the infant's illness; the probability that such perfect concordance occurred by chance is less than 1 in 10 billion. *C. botulinum* spores have been found in honey from the United States, Argentina, Australia, Canada, China (Taiwan also), Denmark, Finland, Italy, Norway, Spain, Japan, and Central America,* but not in honey from the United Kingdom.[16] For these reasons and because honey is not nutritionally essential, all major pediatric, public health, and honey industry agencies in the United States have joined in the recommendation that honey not be fed to infants. In 2000, several honey brands sold in the United States began to carry a warning to not feed honey to infants; an equivalent label first appeared on British honey in 1996.

Discussion of the possible role of corn syrup in infant botulism is necessitated by two reports. In 1982, the U.S. Food and Drug Administration (FDA) found *C. botulinum* type B spores in approximately 0.5 percent (5 of 961) of previously unopened retail samples of light and dark corn syrup[44]; the manufacturer then made changes in the production process. In 1989, the CDC reported a 2-year epidemiologic study of U.S. cases from all states except California.[80] By subgrouping patients by age and using logistic regression modeling techniques, researchers were able to obtain a statistical association between the triad of corn syrup exposure, breast-feeding, and an age of 2 months or older at onset.[61, 80]

In contrast to these reports, a 1988 Canadian survey found no *C. botulinum* spores in 43 corn syrup samples.[37] A 1991 FDA market survey of 738 syrup samples (354 of which were light corn syrup and 271 were dark corn syrup) concluded that none contained *C. botulinum* spores.[46] A California study (unpublished) of 103 corn syrup samples, 72 of which had been fed to infants who subsequently became ill with infant botulism, did not find *C. botulinum* in any sample. In addition, a 1979 epidemiologic study that simply compared corn syrup exposure rates in 41 cases and 107 control infants identified feeding of corn syrup as a significant protective factor against the acquisition of type A infant botulism.[11] The explanation offered for the latter observation was that if a parent chose corn syrup as a sweetener for the infant, honey was unlikely to have been fed to the child as a second sweetener. Thus, on the basis of evidence presently available, corn syrup does not appear to be a source of *C. botulinum* spores or a risk factor for the acquisition of infant botulism. In addition to corn syrups, honey and hundreds of traditional and nontraditional infant food items, including formula milk, have been examined and found to not contain *C. botulinum*.[43]

Besides honey, potential environmental sources of *C. botulinum* spores have been identified in many locales. Soil in Pennsylvania,[48] soil and cistern water in Australia,[57] and soil and vacuum cleaner dust[7] obtained from case homes in California were found to contain *C. botulinum*, the toxin type of which (A or B) in each instance matched that of the ill infant. However, despite the foregoing findings, it deserves emphasis that for most cases of infant botulism, no source of *C. botulinum* spores is ever identified, even circumstantially. In these cases, the illness probably was acquired by swallowing spores adherent to airborne microscopic (invisible) dust.

Clinical Manifestations

Like other infectious diseases, infant botulism produces a spectrum of clinical severity.[2, 7, 10, 48, 65, 72, 79, 90] To date, almost all recognized infants have been sufficiently hypotonic and weak to need hospitalization. Consequently, the present picture of infant botulism is derived from hospitalized patients. However, botulinism in outpatient infants who displayed only a few days of lethargy, poor feeding, and some decrease in the

*See references 9, 11, 15, 37, 40, 44, 52, 69, 85.

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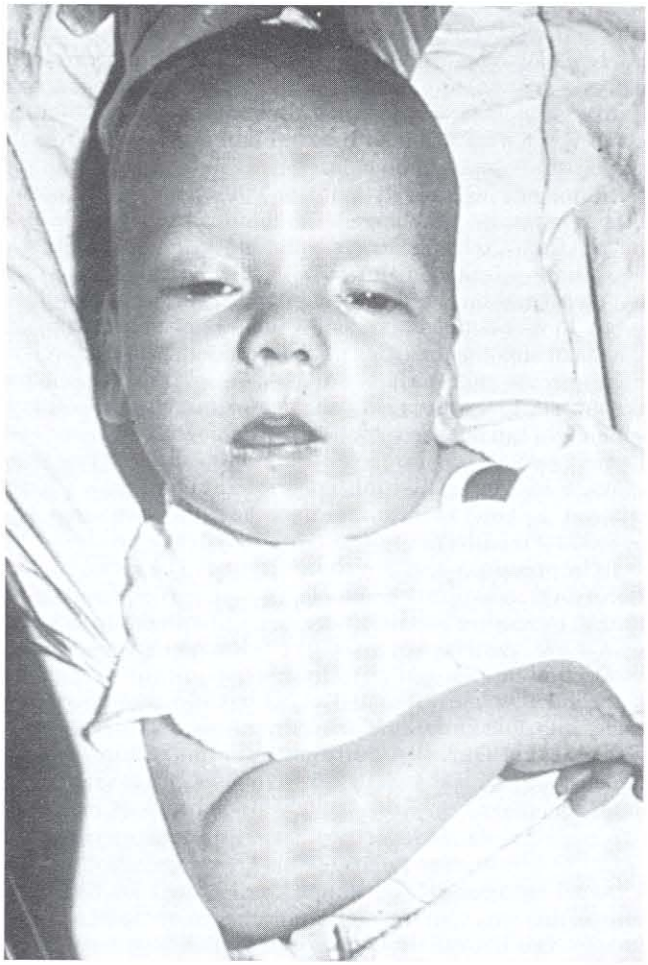

FIGURE 153–2 ■ Mildly affected, 7-week-old infant with botulism. Note the minimal signs, including ptosis, mildly disconjugate gaze, expressionless face, slack jaw, and neck and arm hypotonia.

frequency of bowel movements has been detected by alert physicians familiar with the more "classic" illness. At the opposite end of the clinical spectrum are the few patients with histories and manifestations indistinguishable from those of typical cases of sudden infant death syndrome (crib death),[10, 65, 79, 90] approximately 1 in 20 of which (in California) appears to result from fulminant infant botulism.[7, 10]

The onset of infant botulism ranges from the insidious to the abrupt. At one extreme are patients who were nursing normally 6 hours before becoming so floppy that acute meningitis was the initial diagnosis, and at the other extreme are patients who returned to their physicians four times in a week as the signs of illness gradually became evident.

In the "classic" case, the first sign of illness almost always is constipation (defined as 3 or more days without defecation in a previously regular infant), yet the constipation often is overlooked. A few patients (<5%) will not have a history of constipation. Usually, a mother first notices listlessness, lethargy, and poor feeding, together with breast engorgement if the infant had been nursing. The increasing weakness during the ensuing 1 to 4 days typically brings the baby to medical attention.

Botulism is manifested clinically as a symmetric, descending paralysis. Early in the course, weakness and hypotonia characterize the illness, and the remainder of the physical examination not involving the neuromuscular system is normal. The first signs of illness are found in the cranial nerves; *it is not possible to have infant botulism without having bulbar palsies.* The typical patient has an expressionless face, a feeble cry, ptosis (evident when the eyelids must work against gravity), poor head control, and generalized weakness and hypotonia (Fig. 153–2). Eye muscle paralysis varies, and the pupils often are midposition and initially briskly reactive (Table 153–2). The gag, suck, and swallow reflexes are impaired, as is the corneal reflex if it is tested repetitively. Deep tendon reflexes often are normal at initial evaluation and diminish subsequently as the paralysis extends and increases. The "frog legs" sign frequently is seen. Patients are afebrile unless a secondary infection (e.g., aspiration pneumonia) is present.

The results of most laboratory and clinical studies are normal. At admission, evidence of mild dehydration and fat mobilization may be present because of diminished oral intake. Occasionally at admission, the cerebrospinal fluid (CSF) protein concentration becomes elevated because of the mild dehydration. If infant botulism is suspected soon after admission, electroencephalography, computed tomography, and magnetic resonance imaging seldom are required, but if performed, these examinations yield nonspecific or normal results. Electromyography may offer rapid bedside confirmation of the clinical diagnosis (see "Differential Diagnosis and Diagnosis").[24, 27]

Small amounts (<5 mouse median lethal doses [LD_{50}]/mL) of botulinum toxin occasionally may be identified in serum specimens if they are collected early in the illness.[14, 36, 64, 88, 92] In one report, almost one patient in eight had toxin demonstrable in serum.[36] The definitive diagnostic laboratory study is examination of feces for the presence of *C. botulinum* organisms and toxin, which is the only way to identify the neurotoxin type (A, B, or other) responsible for the illness. Clinically suspected cases that lack an identified toxin type are not included in official tallies of infant botulism.[20, 21]

The usual hospital course of untreated infant botulism has certain general features.[43, 48, 72] After the increasing weakness has necessitated admission, the weakness and hypotonia continue to progress and usually become generalized. The deep tendon reflexes, which may be normal at admission, may diminish or disappear temporarily. The

TABLE 153–2 ■ NEUROLOGIC SIGNS HELPFUL IN THE DIAGNOSIS OF INFANT BOTULISM

Test	Findings
1.	Take the patient to a dark room. Shine a bright light into the eye; note the quickness of pupillary constriction. Remove the light when the constriction is maximal; let the pupil dilate again. Then immediately repeat the light, continuing thus for 1 to 3 minutes. The initially brisk pupillary response may become sluggish and the pupil unable to constrict maximally. (Fatigability with repetitive muscle contraction is the clinical hallmark of botulism.)
2.	Shine a bright light onto the fovea and keep it there for 1 to 3 minutes, even if the infant tries to deviate the eyes. Latent ophthalmoplegia may be elicited, and/or purposeful efforts to avoid the light may diminish.
3.	Place a clean fifth finger in the infant's mouth while taking care to not obstruct the airway. Note the strength and duration of the reflex sucking. The suck is weak and poorly sustained. The gag reflex strength also may be quickly checked (if the infant has not been fed recently).

Adapted from Arnon, S. S.: Infant botulism. Annu. Rev. Med. *31*: 541–560, 1980. Reproduced with permission from Annual Reviews, Inc.

TABLE 153–3 ■ COMPLICATIONS OF INFANT BOTULISM

Adult respiratory distress syndrome
Aspiration
Clostridium difficile colitis
Fracture of the femur (nosocomial)
Inappropriate antidiuretic hormone secretion
Misplaced or plugged endotracheal tube
Necrotizing enterocolitis
Otitis media
Pneumonia
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Tension pneumothorax
Transfusion reaction
Urinary tract infection
Subglottic stenosis
Tracheal granuloma
Tracheitis
Tracheomalacia

TABLE 153–4 ■ WORKING DIFFERENTIAL DIAGNOSIS OF INFANT BOTULISM

Admission Diagnoses	Subsequent Working Diagnoses
Rule out sepsis	Hypothyroidism
Dehydration	Metabolic encephalopathy
Viral syndrome	Amino acid metabolic disorder
Pneumonia	Heavy metal poisoning (Pb, Mg, As)
Idiopathic hypotonia	Drug ingestion
Failure to thrive	Poliomyelitis
	Medium-chain acyl-CoA dehydrogenase deficiency
	Brain stem encephalitis
	Myasthenia gravis
	Viral polyneuritis
	Guillain-Barré syndrome
	Hirschsprung disease
	Werdnig-Hoffmann disease

nadir of paresis and paralysis in untreated patients usually occurs within 1 to 2 weeks after admission; such patients often remain at their nadir for as long as 1 to 3 weeks before showing signs of improvement. However, once strength and tone begin to return, improvement continues steadily and gradually over the ensuing weeks in the absence of complications (Table 153–3).

In the California experience, infant botulism does not have a biphasic or relapsing course, and perceived "relapses" have been found, in retrospect, to be an indication of either the onset of a complication (see Table 153–3) or premature discharge. However, the clinical experience elsewhere with regard to relapses has been different.[32, 68, 72] The patient is ready for discharge when the gag, suck, and swallow reflexes are sufficiently strong to both protect the airway against accidental aspiration and ensure the adequacy of oral intake. Parents also may be taught to feed by gavage at home. In either situation, discharge may occur safely while head lag and constipation are still present.

Differential Diagnosis and Diagnosis

When initially brought to medical attention, patients with infant botulism often are so mildly weak and hypotonic that the illness is not suspected. Even today, more than 25 years after initial recognition of the disease, suspected sepsis remains the most common admission diagnosis for patients with infant botulism. A careful history (constipation commonly is overlooked) and physical examination (especially cranial nerve function) usually provide sufficient information for correct identification of infant botulism and render most additional testing for the other entities typically suspected unnecessary (Table 153–4).

The diagnosis of infant botulism is established by identification of *C. botulinum* organisms in the feces of an infant with clinical signs consistent with the paralyzing action of botulinum toxin.[20, 43, 45, 51, 63] Extensive studies have demonstrated that *C. botulinum* is not part of the normal resident flora of infants or adults.[7, 36, 81, 82] If the fecal specimen is obtained sufficiently early in the course of the illness, it also will contain botulinum toxin. Because of the patient's constipation, an enema with sterile, nonbacteriostatic water (not saline) commonly is needed to obtain a fecal specimen for diagnostic examination. The mouse neutralization test remains the most sensitive and specific assay for identifying botulinum toxin.[21] Laboratory diagnosis to identify the toxin type responsible for the illness is essential for the case to be registered as infant botulism and is important for prognosis; the mean hospital stay is significantly longer in untreated type A cases (see "Treatment").[2] Physicians are reminded that in most states, botulism or suspected botulism (all types) is an immediately reportable illness.

At the bedside, electromyography sometimes can be helpful in ambiguous situations; when a clinically weak muscle is tested, electromyography often discloses a pattern known by the acronym BSAP (brief, small, abundant motor unit potentials).[9, 24, 27, 30, 72, 75] The edrophonium (Tensilon) test does not need to be performed because congenital myasthenia gravis can be excluded by history, and de novo myasthenia does not occur at this age because of the immaturity of an infant's immune system. Likewise, Guillain-Barré syndrome documented by finding a consistently elevated protein concentration in CSF occurs rarely, if at all, in infancy. In infant botulism, the CSF protein concentration is normal, the occasional exception being that of a specimen collected while the child is dehydrated.

Treatment

Specific therapy for infant botulism is now available. In California, a 5-year, randomized, double-blinded, placebo-controlled treatment trial demonstrated the apparent safety and efficacy of human-derived botulinum antitoxin, known formally as botulism immune globulin intravenous (human) (BIG-IV).[5, 45] The use of BIG-IV reduced the mean hospital stay per case from approximately 5.5 weeks to approximately 2.5 weeks ($p < .001$), as well as the mean hospitalization cost per case by approximately $70,000 ($p < .001$). Treatment with BIG-IV should be started as early in the illness as possible. In the United States, BIG-IV may be obtained from the California Department of Health Services (24-hour telephone: 510-231-7600) under a U.S. FDA–approved Treatment Investigational New Drug (IND) protocol; the license application for BIG-IV is under review at the FDA.

Successful management of infant botulism also depends on meticulous supportive care and anticipation and avoidance of potentially fatal complications (see Table 153–3). Feeding and breathing generally require the most attention. At admission, patients should undergo cardiac, respiratory, and transcutaneous blood gas monitoring (especially carbon dioxide pressure) until it is clear that the paralysis no longer is progressing. An endotracheal tube often is needed to

maintain and protect the airway, even in the absence of a need for mechanical ventilation. Particular care should be taken to protect the patient from the acquisition of nosocomially acquired *C. difficile* colitis.[71]

A third cornerstone of management is forbearance. Antibiotics should be reserved to treat the principal secondary infections (pneumonia, urinary tract infection, otitis media) because their use may result in lysis of intraintestinal *C. botulinum* and liberation of intracellular neurotoxin into the gut lumen. This potential problem may be avoided by the use of nalidixic acid or trimethoprim-sulfamethoxazole, antibiotics to which *C. botulinum* is known to be resistant.[87]

Performing a tracheostomy is not necessary.[1, 72] Improved airway management can be accomplished by two simple positioning measures. First, for expansion of the thoracic cage and assistance in diaphragmatic function, patients should be placed in an older-style crib, the rigid bottom mattress of which can be lifted to tilt the entire body to a 30-degree angle. Second, for tipping the head back and to maintain normal curvature of the neck and airway, a soft cloth should be rolled to the thickness of approximately three fingers and placed under just the child's neck. This maneuver allows oral secretions to drain away from the trachea into the true posterior pharynx, where they are swallowed most easily.

The use of intravenous feeding (hyperalimentation) is discouraged because of its potential for causing secondary infection and the success obtained with nasogastric or nasojejunal tube feeding. Mother's milk is the nutritional fluid of choice. Isolation measures or "enteric precautions" are not required, but meticulous handwashing is. Soiled diapers should be autoclaved because they can be expected to contain botulinum neurotoxin, as well as viable spores and vegetative cells of *C. botulinum*. For this reason, staff with open lesions on their hands should not handle the diapers.

The hospital stay of all 508 California patients hospitalized between 1976 and 1991 averaged just over 1 month (4.9 weeks). However, the mean length of stay differed significantly ($p < .0001$) between the 307 type A cases (5.7 weeks) and the 201 type B cases (3.6 weeks), in large part because the major complications and multimonth hospitalizations occurred mainly in type A cases. Thus, untreated illness caused by type A toxin appears to be potentially, but not invariably, more severe than that caused by type B toxin. With the use of BIG-IV, the mean hospital stay has been reduced to approximately 2.5 weeks for patients with either type A or type B infant botulism.

Outcome and Prognosis

Recovery from infant botulism occurs through regeneration of the poisoned terminal unmyelinated nerve endings. The newly synthesized nerve twigs then induce the formation of new motor end-plates that are functionally and morphologically indistinguishable from the original ones.[25, 26] In experimental animals and in humans, completion of this process takes several weeks.[26] Consequently, in the absence of hypoxic cerebral complications, full and complete recovery of strength and tone is the expected outcome of infant botulism. In addition, because botulinum toxin does not cross the blood-brain barrier to any functional degree, the child's intelligence and personality remain as originally endowed. Parents often need reassurance on this latter point. Reinfection with the same or a different type of *C. botulinum* toxin has not occurred. In hospitalized patients in the United States, the case-fatality ratio is less than 1 percent, a reflection of and tribute to the high quality of intensive care given to these critically ill infants. In other countries, the experience has not been so fortunate.

Prevention

At present, the one known way to prevent the acquisition of infant botulism is not to feed honey to infants, and all major pediatric and public health agencies have endorsed this recommendation. Breast-feeding may help moderate the rapidity of onset and the severity of illness. Persuasive evidence that links infant botulism to the ingestion of corn or other syrups is lacking. Mean hospital costs in California (1984 to 1991) exceeded $100,000 per case (2001 dollars; data collection began in 1984), and the patient with the most protracted illness was hospitalized for 10 months in 1988 at a cost of more than $1,000,000 (2001 dollars). These economic facts combine with humanitarian considerations to make a compelling case for the prevention and effective treatment of infant botulism.

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